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Attention: James F. Haley, Jr.,
Margaret A. Pierri

JHB/JB/23348
27th November, 1985

Dear Sirs,

US Patent Application 156 910
FTR 913
Our File: 13348

Thank you for your letter of 10th October and telex of 21st November. I have been able to discuss this action with the inventors during my visit to Neuchâtel last week.

The Examiner rejects the claims on the basis of a combination of Gaisch (FTR 848) and the Francis reference. His principal assertion can be found at page 2 line 15 of the action: "it would be obvious...". The inventors point out the process described by Gaisch is of a fundamentally different character from that described by Francis, so that there is no obvious reason to combine the disclosures of the two documents in the manner suggested by the Examiner.

Microorganisms can utilise nitrates in two quite different ways, as can be seen from the enclosed entries in "Dictionary of Microbiology" by Singleton and Sainsbury. FTR 913 exemplifies the first type of process, which is "assimilatory", according to which nitrate is reduced to ammonia, typically under aerobic conditions, and ultimately appears as protein in the biomass. The other process, namely "dissimilatory", occurs under essentially anaerobic conditions and gives gaseous products, with nitrogen gas as the characteristic end product.

The present invention utilises an assimilatory process as in the earlier Gaisch patent, and progressively reduces the nitrates to a substantially zero concentration. The dissimilatory process described by Francis passes through nitrite (-NO_2^-) as an intermediate stage so that, while the nitrate level is reduced, the nitrite level increases for a time. Nitrite as well as nitrate can be disadvantageous in tobacco, and a process in which the total quantity of both these species does not decrease until a very late stage in the reaction is thus disadvantageous and puts some restriction on the practical application of the process.

Apart from the difference in the type of process, which means that it is not a simple matter to combine the teaching of Francis with that of Gaisch, there are other substantial differences. Francis is concerned with the treatment of waste water. He uses naturally occurring organisms, but the same approach cannot be used in a manufacturing process for the production of a specified product, because the result will be too variable. Furthermore, Francis uses very low dilution rates, and consequently low throughputs, and typically does not achieve complete nitrate removal. Thus, with a fermenter of 1 m^3 volume, Francis can treat 30 litres per hour continuously (dilution rate 0.03). In a fermenter of similar size, the present inventors can use dilution rates from 0.1 to 0.35, giving a volume treatment of 100-350 litres per hour, while at the same time obtaining 100% removal of nitrate. Correspondingly, engineering experience in the industry has shown that to carry out an anaerobic process similar to Francis in a continuous manner requires the use of very large fermenters, and that an anaerobic process is more economically operated in the batch or fed batch modes, thus further discouraging any attempt to combine the teachings of Francis with those of Gaisch.

As regards the choice of organism, a number can be used as indicated in the present application. Nevertheless, the choice for the particular circumstances of tobacco treatment is not an obvious one, because many organisms are known to "use nitrate" under certain conditions, but relatively few are successful on the industrial scale in the special conditions of tobacco extract. However, to emphasise this point in support of claims 32 and 33 might suggest to the Examiner that the broad claim should be limited in this direction.

The particular preference for *Candida utilis* in the present case is because it is a yeast closely related to those used already in food processing. Because of this, the use of this particular organism finds ready acceptance in a product ultimately intended for human consumption. The selection of this yeast enables bacteria and relatively unknown organisms to be avoided. On the other hand, many of the *Candida* yeasts themselves cannot be employed for the purposes of the invention, notwithstanding the fact that the reference books quote them as capable of utilizing nitrate. The enclosed extracts from the publication of Van Uden and Buckley show two *Candida* yeasts that cannot be used under the conditions of tobacco extract, along with the entry for *Candida utilis*, which can be used. The capability of assimilating potassium nitrate is similarly indicated in every case.

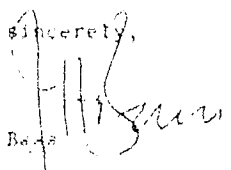
On the question of anti-foam agents, the inventors suggest that the use of anti-foam is not obvious in that most conventional anti-foaming agents are not

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compatible, on the one hand, with the food preparation laws or, on the other hand, with the flavour of the treated tobacco. It is not clear that this represents an answer to the objection, but in any case the use of anti-foam is peripheral to the invention.

If the above does not constitute sufficient basis for an effective reply to the Examiner's arguments, please let us know. Clearly, you may obtain any necessary extension of time.

Yours sincerely,

J. H. B. 

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